[CONTRIBUTION NO. 257 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE INC.]

6,7-DIHYDRO-5*H*-DIBENZ[*c*,*e*]AZEPINE DERIVATIVES, A NEW CLASS OF EPINEPHRINE ANTAGONISTS

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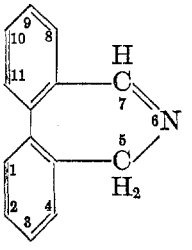
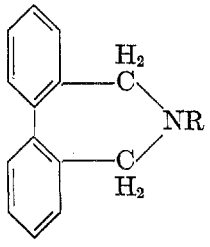
The desire of pharmacologists and clinicians for antagonists against epinephrine has stimulated a search for organic compounds showing such specific anti-epinephrine activity. Of several types of synthetic compounds possessing the desired properties, the most widely investigated are at present the β-haloethyl-amines, the prototype of which is chloroethyldibenzylamine (Dibenamine*) (2, 3). The clinical usefulness of this class of so-called "nitrogen-mustards" is, however, greatly restricted by their unpleasant toxic manifestations (6, 7) which are due to the presence of halogen in an organic linkage similar to that in mustard gas.

In the search for new types of epinephrine antagonists, efforts were therefore directed towards the synthesis of compounds without halogen in organic linkage. As a result of these investigations, a new group of organic amines was found which exhibits potent anti-epinephrine properties.

The new amines are 6-substituted 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepines (II), derived from the ring system I by partial hydrogenation and substitution on the nitrogen. Some of these compounds possess specific anti-epinephrine activity, the degree depending upon the nature of the substituting radical R.



I



II R = R
VIII R = H
X R = $CH_2CH{=}CH_2$
XI R = C_6H_5

The synthesis of the amines is accomplished by reaction of *o*,*o*′-bis(bromomethyl)biphenyl (III) with primary amines. The starting material III was first prepared by Kenner and Turner (5) by direct bromination of *o*,*o*′-bitolyl.

As products of the reaction of III with primary amines, practically only compounds of formula II are obtained. They are listed in Table I. Diamines of formula IV, which theoretically also could be formed, were not found. The tendency to form the seven-membered ring system is so strong that not even secondary amines react to diamines of formula V. In this case the dibenzazepine

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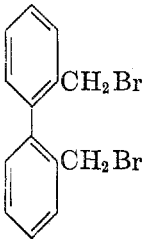
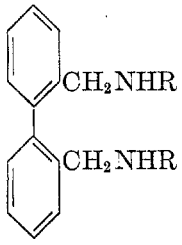
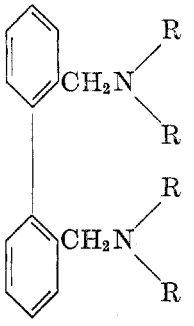
ring system is also formed, obviously by an intramolecular ring closure of the hypothetical first product VI of the reaction, resulting in quaternary derivatives of formula VII. In the case where R is methyl this quaternary derivative was prepared also by reaction of the amine II with methyl iodide.



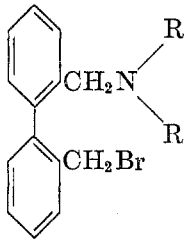
III



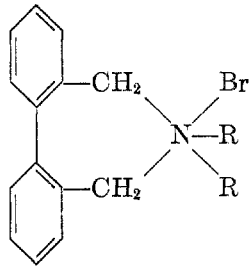
IV



V

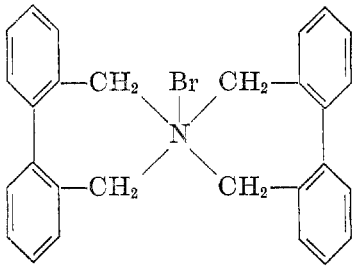


VI



VII

When the dibromide III is reacted with ammonia, only very little of the amine VIII is formed. The major product of the reaction is a quaternary compound, analyzing correctly for the formula $C_{28}H_{24}BrN$. It may have formula IX in analogy to a compound obtained by von Braun and Nelken (1) in a similar manner in the isoindoline series.



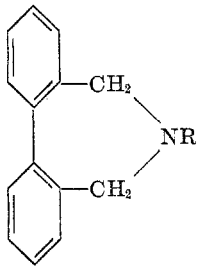
IX

The tertiary amines of formula II are strong bases. They are mostly colorless, water-insoluble liquids which distill without decomposition *in vacuo*. The salts are generally well crystallized. In contrast to aliphatic amines, aniline reacted only slowly with the dibromide III. The resulting derivative XI is a weak base.

The pharmacological tests carried out in our Pharmacology Department by Dr. L. O. Randall and his associates showed anti-epinephrine properties in all compounds where R is a small alkyl group. The most potent amine is 6-allyl-

TABLE I

6-SUBSTITUTED 6,7-DIHYDRO-5*H*-DIBENZ[*c*,*e*]AZEPINES



COMPOUND	R	FORMULA	SALT	M.P., °C.	ANALYSIS	C	H	N
XII	Methyl	$C_{15}H_{15}N$	H_3PO_4	187	Calc'd	58.63	5.90	4.56
					Found	58.35	5.65	4.59
			HBr	223–225	Calc'd	62.08	5.56	4.83
					Found	62.33	5.83	4.61
			Oxalate	173–174	Calc'd	68.20	5.73	
					Found	68.37	6.10	
XIII	Ethyl	$C_{16}H_{17}N$	HBr	203–204	Calc'd	63.16	5.96	
					Found	62.82	6.00	
XIV	*n*-Propyl	$C_{17}H_{19}N$	$HBr \cdot \frac{1}{2} H_2O$	203–204	Calc'd	62.39	6.47	4.28
					Found	62.04	5.96	4.26
XV	Isopropyl	$C_{17}H_{19}N$	HBr	238–240	Calc'd	64.15	6.34	
					Found	64.44	6.37	
XVI	*n*-Butyl	$C_{18}H_{21}N$	$HBr.\frac{1}{2} H_2O$	163–164	Calc'd	63.34	6.79	4.10
					Found	63.50	6.40	4.36
X	Allyl	$C_{17}H_{17}N$	HCl	214–215	Calc'd	75.12	6.67	
					Found	74.87	6.76	
			HBr	212–213	Calc'd	64.56	5.74	4.43
					Found	64.78	5.58	4.35
			H_3PO_4	210	Calc'd	61.21	6.05	
					Found	61.41	6.14	

6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine (X). The detailed pharmacological results will be published shortly in *The Journal of Pharmacology and Experimental Therapeutics*.

The synthesis of the new compounds suffers from the difficult preparation of the bromo compound III. The direct bromination of bitolyl (5) has recently been somewhat improved by Hall, Lesslie, and Turner (4). However, the method is still far from satisfactory. This is shown by the fact that the same authors had to resort to a lengthy synthesis, starting with diphenic acid and involving a lithium aluminum hydride reduction, in order to prepare sufficient quantities of III. Investigations to be described shortly have recently resulted in a synthesis of III suitable for technical purposes.

EXPERIMENTAL

The melting points are uncorrected.

1. *o,o'-Bis(bromomethyl)biphenyl* (III). This compound was prepared essentially according to Kenner and Turner (5). The yields are low, and the purification is lengthy. The pure compound was found to melt at 82–83° (Kenner and Turner: m.p. 87.5°).

Anal. Calc'd for $C_{14}H_{12}Br_2$: C, 49.44; H, 3.56; Br, 46.72.

Found: C, 49.69; H, 3.84; Br, 46.99.

2. *General method for the amines of formula II.* The reaction of the dibromide III with primary amines is best carried out in benzene. One mole of the dibromide is dissolved in about ten times its volume of benzene. The solution is added with stirring at a temperature not exceeding 50° (external cooling) to a solution of 3 moles of the amine in about 15 volumes of benzene. The reaction is not instantaneous, because in experiments where the reactants were mixed at once the temperature started to rise only after a short induction period, depending upon the initial temperature and the particular amine used. When the spontaneous reaction subsides, the mixture is warmed for about an hour to 70–80°. During the reaction the hydrobromide of the excess primary amine crystallizes. After cooling, the hydrobromide is filtered off; the filtrate, containing the new base, is washed with water and extracted with acid to remove non-basic by-products. The bases are liberated with alkali and extracted with ether or benzene. The solutions are distilled to dryness. The crude amines are then purified by vacuum-distillation. An alternate method consists in dissolving the crude base in ether or another suitable solvent and neutralizing the solution with an acid, thereby precipitating the salt which is then purified by crystallization.

For the preparation of the methyl and ethyl derivatives of II the reaction mixtures were kept at temperatures below 30° for the first 3 hours in order to prevent the escape of the low-boiling primary amines. The isolation of the compounds was carried out essentially in the same way as described below for the allyl compound.

When water-insoluble primary amines are used, it is preferable to purify the resulting dihydrodibenzazepine by distillation in order to remove any unchanged starting amine.

As an example of the procedure, the preparation of 6-allyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine (X) is described in detail. The properties of the other amines are listed in Table I.

3. *6-Allyl-6,7-dihydro-5H-dibenz[c,e]azepine* (X). *o,o'*-Bis(bromomethyl)biphenyl (III) (5) (54 g.) is dissolved in 200 cc. of anhydrous benzene. The solution is added dropwise to a stirred solution of 29 g. of allylamine in 200 cc. of benzene. By external cooling the temperature is kept at 45–50°. Shortly after the beginning of the addition, allylamine hydrobromide starts to separate, usually as an oil which soon crystallizes. After complete addition, the mixture is slowly heated up to 70–75° and kept at this temperature for about 1 hour. The mixture is then allowed to cool and stand overnight at room temperature. The crystals are filtered and washed with benzene. The combined filtrates are extracted repeatedly with water. The washings are discarded. The benzene layer is extracted with dilute hydrochloric acid and the combined acid extracts are made alkaline with ammonia. The liberated base is extracted with benzene and the solvent is evaporated at atmospheric pressure, finally in a partial vacuum. The residue is distilled *in vacuo*. Practically the total amount distills within 5°. The boiling point is 176–179°/12 mm. and 131–134°/0.02 mm. The distillate is a colorless oil which is insoluble in water. The yield is about 26 g. (70%).

Phosphate: The distilled base (113 g.) is dissolved in 300 cc. of absolute alcohol. A mixture of 56.5 g. of 85% phosphoric acid and 200 cc. of alcohol is added slowly. The mixture warms up. When undisturbed, crystallization may not start for days. On seeding, the phosphate starts to crystallize within a few minutes. Crystallization is completed by cooling in the refrigerator. The phosphate is filtered and is generally of high purity, giving correct analyses. The yield is approximately 130 g. It may be recrystallized from alcohol and melts at 209–210°. It dissolves easily in water.

Anal. Calc'd for $C_{17}H_{17}N \cdot H_3PO_4$: C, 61.21; H, 6.05.
Found: C, 61.41; H, 6.14.

Hydrochloride: The distilled base (7 g.) is dissolved in 40 cc. of alcohol. Alcoholic hydrochloric acid is added until the mixture is acid to Congo Red. The solution is cooled in the refrigerator. The hydrochloride crystallizes. Recrystallization from alcohol yields the pure compound of m.p. 214–215°. The solubility in H_2O (25°) is about 12%.

Anal. Calc'd for $C_{17}H_{17}N \cdot HCl$: C, 75.12; H, 6.67; N, 5.15.
Found: C, 74.87; H, 6.76; N, 5.41.

Hydrobromide: The distilled base (7 g.) is dissolved in 40 cc. of alcohol. Addition of alcoholic hydrobromic acid precipitates the crystallized hydrobromide which is purified by recrystallization from water where it dissolves to about 2% at 20°. The hydrobromide melts at 213–214°.

Anal. Calc'd for $C_{17}H_{17}N \cdot HBr$: C, 64.56; H, 5.74; N, 4.43.
Found: C, 64.78; H, 5.58; N, 4.35.

4. *6-Phenyl-6,7-dihydro-5H-dibenz[c,e]azepine* (XI). *o,o'*-Bis(bromomethyl)biphenyl (3.4 g.) is dissolved in 50 cc. benzene. Then 3 g. of aniline is added. The reaction proceeds slowly. After standing for 3 days at room temperature, crystals of aniline hydrobromide separate and are filtered. The filtrate is extracted with 20% hydrochloric acid. The extract is made alkaline with ammonia and is repeatedly extracted with ether. The ether solution is neutralized with alcoholic hydrobromic acid, precipitating some resinous material. This is filtered off, and the filtrate is distilled to dryness. The solid residue is recrystallized from alcohol, yielding 6-phenyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine hydrobromide of m.p. 230–232°.

Anal. Calc'd for $C_{20}H_{17}N \cdot HBr$: C, 68.19; H, 4.87; N, 3.97.
Found: C, 68.15; H, 5.34; N, 4.27.

5. *Reaction of o,o'-bis(bromomethyl)biphenyl with ammonia.* Whereas primary and secondary amines react smoothly with *o,o'*-bis(bromomethyl)biphenyl in benzene solution, ammonia scarcely reacts in this solvent. To enable interaction, alcohol or alcohol-ether have to be used as solvents.

(a) *6(7H),6'(7'H)-Spiro-bi{5H-dibenz[c,e]azepinium}bromide* (IX). *o,o'*-Bis(bromomethyl)biphenyl (5.5 g.), dissolved in 50 cc. of ether, is mixed with 50 cc. of 10% methanolic ammonia at 20°. A slight increase in temperature is noticeable, and after about 1 hour, long prisms start to crystallize. They are filtered after standing overnight. The compound is practically insoluble in the common organic solvents and in water. It is recrystallized from 40% formic acid. The salt does not melt up to 310°.

Anal. Calc'd for $C_{28}H_{24}BrN \cdot \frac{1}{2} H_2O$: C, 72.56; H, 5.44; N, 3.02.
Found: C, 72.63; H, 5.59; N, 3.15.

(b) *6,7-Dihydro-5H-dibenz[c,e]azepine* (VIII). The mother liquor of compound IX above is distilled to dryness. The crystalline residue is shaken with ether and dilute ammonia. The ether solution is separated, dried, and neutralized with alcoholic hydrobromic acid. The crystalline hydrobromide is filtered and recrystallized from alcohol, m.p. 283–284°.

Anal. Calc'd for $C_{14}H_{13}N \cdot HBr \cdot \frac{1}{2} H_2O$: C, 58.96; H, 5.30; N, 4.91.
Found: C, 58.70; H, 4.90; N, 5.09.

The *hydrochloride* prepared similarly melts at 286–288°.

Anal. Calc'd for $C_{14}H_{13}N \cdot HCl$: C, 72.56; H, 6.09; N, 6.05.
Found: C, 72.66; H, 6.16.

6. *Quaternary derivatives.* The following derivatives were obtained by reaction of the respective amines with methyl halogenides:

(a) *6,6-Dimethyl-6,7-dihydro-5H-dibenz[c,e]azepinium iodide* (XVII). 6-Methyl-6,7-di-

hydro-5*H*-dibenz[*c*,*e*]azepine (XII) of b.p.$_{10}$ 175–178° (1 g.) and 0.5 cc. of methyl iodide were dissolved in 25 cc. of ether. After a few minutes, long needles of the quaternary iodide started to separate. Recrystallization from alcohol gave the pure compound of m.p. 287–288°. It is almost insoluble in water.

Anal. Calc'd for $C_{16}H_{18}IN$: C, 54.71; H, 5.16.
Found: C, 54.93; H, 5.23.

(b) *6,6-Dimethyl-6,7-dihydro-5H-dibenz[c,e]azepinium bromide* (XVIII). 6-Methyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine (XII) (2 g.), dissolved in 30 cc. of ether, and 2 g. of methyl bromide in 20 cc. of methanol are mixed and kept at room temperature for 24 hours. The mixture becomes turbid, and a colorless oil soon separates. It immediately crystallizes on scratching. Recrystallization from methanol-ether yields the pure quaternary bromide, m.p. 276–277°.

Anal. Calc'd for $C_{16}H_{18}BrN$: C, 63.16; H, 5.96; N, 4.61.
Found: C, 63.35; H, 6.20; N, 4.93.

(c) *6-Methyl-6-allyl-6,7-dihydro-5H-dibenz[c,e]azepinium iodide* (XIX). The allyl compound (X) (3 g.), was dissolved in 20 cc. of methanol, and 2 cc. of methyl iodide was added. The solution warmed up slightly. After 5 hours, ether was cautiously added, precipitating almost colorless crystals. Recrystallization from alcohol gave the pure compound of m.p. 182–184°. It contains one-half mole of water of crystallization.

Anal. Calc'd for $C_{18}H_{20}IN \cdot \frac{1}{2} H_2O$: C, 56.02; H, 5.48; N, 3.62.
Found: C, 55.97; H, 4.82; N, 3.51.

7. *Reaction of o,o'-bis(bromomethyl)biphenyl with a secondary amine.* *o,o'*-Bis(bromomethyl)biphenyl (20 g.) is dissolved in 150 cc. of benzene. In one portion a solution of 11 g. of dimethylamine in 60 cc. benzene is added. The mixture warms up. When it reaches 50°, the solution is cooled and a sticky precipitate forms. After 15 hours, the benzene is decanted. The residue crystallizes on shaking with propanol-2. Repeated recrystallization from propanol-2 yields the semihydrate of m.p. 274–276°.

Anal. Calc'd for $C_{16}H_{18}BrN \cdot \frac{1}{2} H_2O$: C, 61.35; H, 6.11; N, 4.47.
Found: C, 60.91; H, 6.05; N, 4.69.

When dried at 100° *in vacuo*, the water of crystallization is removed. The melting point does not change.

Anal. Calc'd for $C_{16}H_{18}BrN$: C, 63.16; H, 5.96; N, 4.61.
Found: C, 63.01; H, 5.77; N, 4.68.

The compound is identical with XVIII (Exp. 6b above).

Acknowledgment. I am indebted to Dr. Al Steyermark for the microanalyses reported in this paper.

SUMMARY

6,7-Dihydro-5*H* dibenz[*c*,*e*]azepine derivatives, a new group of amines containing a seven-membered heterocyclic ring system, are described. Several representatives of this class of compounds, especially the N-allyl derivative, exhibit potent anti-epinephrine effects.

NUTLEY, NEW JERSEY

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